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# Title Page

**Title**: Macroscopic assessment of the quality of cold perfusion after deceased-donor kidney procurement: A United Kingdom population-based cohort study.

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**Data Statement:**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Concern regarding the quality of cold perfusion (QOP) during macroscopic assessment of procured kidneys is a common reason for discard. In the UK, QOP is routinely graded by both retrieving and

implanting teams during back-bench surgery as: 1 (good), 2 (fair), 3 (poor) or 4 (patchy). We evaluated the association of this grading with organ utilisation, graft outcomes and agreement between teams. Data on all deceased-donor kidneys procured between January 2000 and December 2016 were analysed for discard rates, whilst association with graft outcomes was studied in single adult transplants. Of 31,167 kidneys procured, 90.6%, 5.7%, 1.7% and 2.1% were assigned grades 1, 2, 3 and 4, respectively at retrieval. QOP was an independent risk factor of discard, with the highest rates observed in grade 3 kidneys (41.8%), compared to 6.5% in grade 1 (aOR 7.67, 95% CI 5.44-10.82, p<0.001). Grading at retrieval was an independent predictor of delayed graft function (p=0.019) and primary non-function (p=0.001), but not long-term graft survival (p=0.111). Implanting grade was an independent predictor of all three outcomes (p<0.001, p<0.001 and p=0.002 respectively). Consistency of grading between teams was poor (Kappa=0.179). QOP influences utilisation and predicts outcomes, but a standardised and validated scoring system is required.

# 1 | Introduction

Despite the on-going shortage of kidneys for transplantation, a significant number of organs continue to be discarded after procurement. In the UK, discard rates range from 10-12%, with rates of up to 20% in the US.[1] Marginal and donation after circulatory death (DCD) donor kidneys are more susceptible, with reported discard rates of around 50%.[2] Although discard of a small proportion of organs is inevitable, evidence suggests that, in some cases, potentially usable kidneys are being discarded.[3, 4] The reasons for discard are multiple, complex, and compounded by a lack of established tools for viability assessment.[5, 6] Donor risk indices and pre-implantation histological scoring have been incorporated into some transplant programs,[7] but lack universal approval, and the latter may even lead to inappropriate discards.[8] Improved understanding of objective markers that affect outcomes (e.g. donor age and cold ischaemia time) have led to changes in allocation and utilisation.[9] However, more granular and subjective factors that continue to influence decision-making and graft outcomes remain poorly understood.[10] One such factor is the macroscopic assessment of quality of cold perfusion (QOP) of procured kidneys.

Macroscopic assessment is routinely performed by surgical teams and forms a crucial element of post-procurement decision-making.[5] Inspection involves assessment for retrieval damage, anatomical abnormalities and QOP. Previous national registry studies have explored factors associated with retrieval damage of kidneys, but overlooked the effects of perfusion defects on organ utilisation and outcomes.[11, 12] Most transplant programs require the retrieving surgeon to comment on the QOP,[13] but it remains a poorly defined entity, with no validated categorisation and/or quantification.[14] Studies have shown that considerable disagreement can exist in assessing QOP, even amongst experienced surgeons within the same centre.[15, 16] QOP is generally accepted as the subjective assessment of the differential colour staining or discolouration across the surface of the kidney. A well perfused kidney should have a uniformly pale appearance, whilst a poorly perfused kidney may be patchy or globally purple.[17]

In the United Kingdom (UK), each procured deceased-donor kidney is routinely graded on its QOP by the retrieval team. This grade is communicated to the implanting team before final

acceptance. If the kidney is subsequently transplanted, the implanting team will also grade the perfusion during back-bench preparation. This study sought to use this existing information to explore three main questions with regard to macroscopic assessment of QOP:

1) Does the QOP at retrieval influence the decision to discard organs?

2) Do the retrieving and implanting teams give consistent perfusion grades?

3) Is the QOP at either retrieval or implantation independently associated with graft outcomes (delayed graft function, primary non-function and graft survival)?

# 2 | Methods

## 2.1 | Study Population

Data were obtained from the National Health Service Blood and Transplant (NHSBT) database for all deceased-donor kidneys retrieved in the UK between January 2000 and December 2016. Organs were excluded in a stepwise approach, in order to perform various analyses, and details of these exclusions and the resulting sample sizes are depicted in Figure 1. Initially, the association between the QOP grade assigned by the retrieval team and discard rates was assessed, which included all retrieved kidneys in the analysis. Kidneys that are discarded after retrieval (either before or after travelling to recipient centre) are not routinely given a second QOP grade by the implanting team; hence, these were excluded from subsequent analysis. For analysis of the consistency of the QOP grading between retrieving and implanting teams, those kidneys that underwent machine perfusion were additionally excluded, as were those that did not have a QOP grade assigned by both teams. Analyses of the associations between QOP and graft outcomes in transplanted kidneys excluded paediatric recipients (<18 years), and recipients of multi-organ or antibody-incompatible transplants.

The project was registered as an audit with University Hospitals Birmingham NHS Trust (audit code: CARMS-15648) and approved by NHSBT.

## 2.2 | Quality of Perfusion

During the study period, standard practice was for the QOP, anatomy (number and orientation of vessels, ureters or abnormal lesions), retrieval damage, timing and type of perfusion fluid used to be documented by the retrieving team. This is ordinarily performed during back-bench surgery, after an adequate amount of perinephric fat has been removed to reveal the parenchyma. The QOP of each kidney is graded as good = 1, fair = 2, poor = 3 or patchy = 4. Findings are communicated to the implanting team before final acceptance. The implanting team performs the same assessment during back-bench surgery before a final decision to use the kidney. The primary reason for discard is also routinely documented, where applicable. Of note, pre-mortem donor heparinisation is not performed in the UK.

## 2.3 | Definitions

Cold ischaemia time (CIT) was defined as time from the start of cold perfusion to reperfusion after implantation. The donor risk index used was based on the one developed by Watson et al.[18] Delayed graft function (DGF) was defined as need for dialysis within the first 7 days post-transplantation, with grafts that never functioned being classified as having primary non-function (PNF). Graft survival was defined as the time from transplantation to graft nephrectomy, return to dialysis, or death, with patients being censored at the end of follow up. In addition, the outcome of "long-term graft survival" was assessed, which excluded those patients with PNF, and those that either died, developed graft nephrectomy, returned to dialysis or were lost to follow-up within 30 days of transplant.

## 2.4 | Statistical analysis

### 2.4.1 | Discard rates

Multivariable analysis was performed, to assess whether QOP measured by the retrieving team was an independent predictor of organ discard. Prior to this analysis, goodness-of-fit testing was performed for continuous factors using Hosmer–Lemeshow tests, with variables divided into categories based on the quartiles of the distribution if poor fit was detected. A binary logistic regression model was then produced, with the QOP grade entered into the model at the first step, and a backwards stepwise approach to select independent predictors of discard rates for inclusion. Initially, a complete-cases model was produced, which only included those patients with data recorded for all factors being considered. To prevent excessive exclusions of cases, factors with >50% missing data were excluded from this analysis, whilst factors with >10% missing data were included in the initial analysis, but were subsequently excluded if not selected for inclusion by the stepwise procedure. The factors considered for inclusion in the model are detailed in Table S1.

In addition to the complete-cases analyses, a sensitivity analysis was performed, which used a replace-with-mean approach to maximise the number of cases included. For this analysis, missing

values for factors other than the perfusion grade were replaced with the mean for continuous factors, or the mode for nominal factors. The results of the replace-with-mean analyses were then compared to the primary complete-cases analysis, to assess whether findings were consistent.

### 2.4.2 | Outcomes by QOP grade

Initially, a range of factors were compared across the QOP grades. To account for the fact that the grades were ordinal, analyses were performed using Jonckheere-Terpstra tests for continuous factors and Kendall's tau for ordinal factors, with nominal variables being analysed using Chi-square tests. Graft survival was initially analysed using Kaplan-Meier curves. However, this showed that the relatively high rate of PNF in some groups meant that short-term graft failure rates were high, resulting in the assumption of proportional hazards being broken. As such, analyses of graft survival were repeated for the outcome of "long-term graft survival", which excluded those patients with PNF, and those that either died, developed graft nephrectomy, returned to dialysis or were lost to follow-up within 30 days of transplant.

Multivariable analysis was then performed, using binary logistic regression models for the outcomes of DGF and PNF, with Cox regression models used for long-term graft survival. Analyses of DGF excluded patients with PNF, whilst analysis of long-term graft survival made exclusions as previously described. Variable selection was performed using a backwards stepwise approach, as previously described. For analyses of the QOP at retrieval, only factors that would be known at this time were considered for inclusion (i.e. donor factors), and the complete-cases model was reported as the primary analysis. Analyses of the QOP by the implanting team considered all factors for inclusion (i.e. adding recipient and transplant-related factors), with the replace-with-mean models reported as the primary analyses, to maximise the included sample size. A full list of factors considered for inclusion in each analysis is reported in Table S1.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p<0.05$ deemed to be indicative of statistical significance throughout.

# 3 | Results

During the study period, a total of 31,167 kidneys were retrieved from 15,750 donors. At the time of retrieval, QOP was recorded for a total of 30,808 (98.8%) organs, of which 90.6% (n=27,915) were classified as grade 1; 5.7% (n=1,752) grade 2; 1.7% (n=509) grade 3; and 2.1% (n=632) grade 4, respectively.

## 3.1 | Discard rates

A total of 2,556 (8.2%) retrieved kidneys were discarded, with the most common primary reasons being poor perfusion (15.0%), anatomical issues (13.6%) and organ damage (9.0%). Discard rates differed significantly with the QOP at retrieval ($p<0.001$), increasing from 6.5% at grade 1 to 17.6% and 41.8% at grades 2 and 3, respectively. However, discard rates were lower (27.1%) for organs with perfusion grade 4 ('patchy') at retrieval. Multivariable analysis identified a number of independent predictors of organ discard, including increasing donor age and creatinine, as well as DCD donations, whilst kidneys where the liver was retrieved at the same time, and those from donors that died of trauma had significantly lower discard rates (Table 1). After accounting for these factors, the association between QOP and discard rates remained significant ($p<0.001$). As per the univariable analysis, discard rates increased progressively from grade 1 to grade 3, before declining at grade 4.

## 3.2 | Consistency of organ grading

Of the transplanted kidneys, QOP was reported by both retrieval and implanting teams in n=24,105 (96.2%) cases. The consistency of grading was poor, with a quadratic weighted Kappa statistic of 0.169. Whilst the majority of organs with grade 1 at retrieval retained this grade at the implanting centre (88.1%), consistency of grading for higher grade (2-4) organs was low, ranging from 17.6% - 26.2% (Figure 2). For kidneys classified as grade 2-4 at retrieval, the majority were upgraded to a better grade by the implanting team, with 64.5% of these increasing to QOP grade 1.

### 3.3 | Factors associated with QOP at the implanting centre

QOP was recorded by the implanting team in n=23,035 (96.9%) of the transplanted kidneys meeting the inclusion criteria for this analysis (Figure 1), of which 86.2% (n=19,845) were assigned grade 1, 9.5% (n=2,187) grade 2, 2.0% (n=464) grade 3 and 2.3% (n=539) grade 4. Of the donor factors considered (Table 2a/b), increasing age, BMI, terminal creatinine, final temperature, last pre-donation systolic blood pressure, donor risk index and length of stay were associated with significantly poorer QOP grade. Kidneys assigned poorer grading by the implanting team were transplanted into recipients that were significantly older, more likely to be male and on haemodialysis, and with higher BMI and rates of diabetes (Table 2a/b). Analyses using the QOP assigned by the retrieval team returned similar results (data not shown).

### 3.4 | Outcomes based on QOP

On univariable analysis, rates of initial graft dysfunction differed significantly across QOP grades, as assigned both by retrieval and implantation teams ($p<0.001$, Table 3). More specifically, rates of DGF increased markedly between grade 1 and grade 2, with marginal increases across the subsequent grades, whilst rates of PNF increased progressively from grade 1 to grade 3, before declining at grade 4. The QOP grade assigned by the retrieval team was not found to be significantly associated with the outcome of long-term graft survival (i.e. after excluding graft failures within 30 days, $p=0.454$, Figure 3b). However, QOP grade denoted by implantation team was associated with long-term graft survival ($p<0.001$, Figure 3d), with graft survival declining progressively between grade 1 and grade 3 ($p=0.001$), but no significant difference detected between grade 1 and grade 4 organs ($p=0.326$).

Multivariable analyses were then performed, to assess the association between QOP and graft outcomes, after accounting for the effects of potentially confounding factors (Table 4, Table S3a-c, Table S4a-e). Analysis of QOP assessed by the retrieval team only adjusted for those factors that would be known at the time that the kidney was retrieved, to assess whether QOP could improve predictive accuracy over and above the other information available to the retrieval team (Table S1). After adjustment for these factors, the rates of the DGF were found to increase significantly from grade 1 to grade 2 (adjusted odds ratio [aOR]: 1.28, 95% CI: 1.06 – 1.54,

p=0.009). However, no significant increase in the risk of DGF was observed in grade 3 (p=0.292) or grade 4 (p=0.090) organs, with these groups having similar risk to that of grade 2 organs. Analysis of PNF showed a significant progressive increase from grade 1 to 3, but no significant difference was detected between grade 1 and 4 organs (p=0.371). As per the univariable analysis, long-term graft survival was not found to differ significantly across the QOP grades assigned by the retrieval team after multivariable adjustment for confounding factors (p=0.111).

Multivariable analyses of the QOP measured by the implanting team additionally adjusted for the recipient and transplant-related factors that would be known at this time (Table S1). This analysis found the risk of DGF to increase progressively across the QOP grades (p<0.001), with the largest difference being between grade 4 and grade 1 organs (aOR: 2.08, 95% CI: 1.69 – 2.54, p<0.001). Analysis of PNF found in the risk to be significantly higher in QOP grades 2-4, relative to grade 1, but with the highest risk observed in QOP grade 3 kidneys (aOR: 3.65, 95% CI: 2.55 – 5.23, p<0.001). Unlike when measured at retrieval, the QOP measured by the implanting team was found to be a significant independent predictor of long-term graft survival (p=0.002). Compared to grade 1 organs, long-term graft survival was found to be significantly shorter in QOP grade 2 (adjusted hazard ratio [aHR]: 1.18, 95% CI: 1.06 – 1.31, p=0.003) and grade 3 (HR: 1.36, 95% CI: 1.09 – 1.69, p=0.007) organs, but not in those of QOP grade 4 (aHR: 1.04. 95% CI: 0.83 – 1.29, p=0.749).

## 4 | Discussion

Subjective concern over the QOP of procured deceased-donor kidneys is the most common reason for discard (15%) in the UK. This objective analysis, to our knowledge the largest study on this factor, confirms that macroscopic assessment of the QOP has an independent effect on organ utilisation, and can be used to predict short and long-term graft outcomes. Our key findings are; 1) grade 3 (poor perfusion) kidneys are over 6 times more likely to be discarded than grade 1 (good perfusion) kidneys when assessed immediately after retrieval; 2) there is poor consistency between retrieval and implantation macroscopic assessment of kidney perfusion, 3) QOP measured by the implanting team is superior to that measured by the retrieval team for predicting short and long-term outcome, and should be considered during decision-making, patient counselling and risk assessment.

The impact of QOP on organ utilisation is poorly reported, with studies primarily based on single-centre series of discarded kidneys only. In a study of 20 nationally discarded kidneys in the UK, Callaghan et al. observed poor perfusion was the most common reason for discard (25%).[15] In a follow-up study, after the introduction of a national fast-track offering scheme for hard-to-place deceased-donor kidneys, Mittal et al. observed that 22.6% (7/31) of discarded kidneys were not implanted due to poor perfusion.[16] In the US, Narvaez et al. evaluated 456 hard-to-place kidneys offered to a single-centre, and observed 11% of discarded kidneys had visual signs of perfusion defects which, on multivariable analysis, was significantly associated with discard (aOR 2.76, 95% CI, 1.48-5.12).(10) Our study supports these findings, demonstrating an independent effect of QOP alone on discard rates, with odds of discard based on discrete grades.

Interestingly, discard rates for grade 4 organs was similar to grade 2 organs, which may reflect the subjective nature of the terms ‘fair’ (grade 2) and ‘patchy’ (grade 4). Alternatively, grade 4 kidneys may represent high-quality kidneys that have been poorly perfused during retrieval (e.g. aortic cannulae being placed too cranially). These results suggest that further work is required to refine the current grading scale. Recently, Ayorinde et al. have developed a pre-implantation, objective macroscopic scoring system (Cambridge Kidney Assessment Tool, CKAT).[14] Of the

variables included in their system, the quality of the Carrel patch and the perfusion grade were found to be independently associated with organ utilisation. These two variables, when combined, performed better than independent consultant surgeon in predicting utilisation, and correlated well with 1-year graft survival. The authors advocated the development of a common language to aid assessment and prevent inappropriate discards.

The prognostic value of macroscopic assessment on eventual graft outcomes in the recipient is poorly understood. Kidneys with sub-optimal perfusion are intuitively expected to have inferior graft outcomes, yet data to support this is limited. Berardelli et al. applied a complex macroscopic scoring system to select kidneys from older (age > 60 years) donors, and found that 3-year graft survival was similar to that of 'ideal' (age 11 – 49 years) donors.[19] The authors concluded macroscopic assessment obviated need for histological assessment and reduced cold ischaemia time, but their scoring system remains unvalidated. More recently, Tiere et al. undertook a single-centre, prospective study of 166 transplanted kidneys and correlated the macroscopic assessment of QOP by the procurement surgeon with immediate graft function, DGF and PNF.[20] In addition to other macroscopic variables, the surgeon graded the perfusion on a scale of 1 (poor) to 10 (excellent). Multivariable analysis showed QOP was significantly associated with these short-term outcome measures. The authors suggested that these kidneys may benefit from machine perfusion and should be incorporated into multi-variable scoring systems to aid decision-making. Our study supports these recommendations with data from a national perspective.

Early graft loss can have catastrophic effects on patient survival.[21] We demonstrated that QOP at both time points is independently associated with PNF, with the grade measured by the implanting team being the stronger predictor. When considering DGF alone, poorer grades had significantly higher rates, with 44.5% of kidneys classified as QOP grade 4 by the implanting team developing DGF, compared to 25.7% of grade 1 kidneys ($p<0.001$). Given that DGF is associated with short-term morbidity in all deceased-donors, and with graft survival in DBD kidneys, [22] early recognition of kidneys prone to DGF may help decide on appropriate pre-implantation optimisation and post-operative planning.[23] Our study is the first to consider the effect of QOP

on long-term graft survival. Whilst the QOP classified by the retrieval team was not found to be significantly predictive of this outcome (p=0.111), the QOP from the implanting team was found to be a significant independent predictor of outcome (p=0.002), with an adjusted hazard ratio of 1.36 (95% CI: 1.09 – 1.69) for grade 3 vs. grade 1 organs.

These findings should be considered during pre-implantation donor quality assessment and optimisation. A number of donor risk indices (DRIs), combining multiple donor and/or pre-transplant factors, have been used to assess donor quality, but lack sufficient predictive power.[18] Further work is required to ascertain the value of a kidney risk index including factors such as the quality of perfusion and renal artery atherosclerosis. The combination of donor and kidney factors may provide a better decision-making model. Indeed, poorly perfused kidneys with otherwise favourable factors may be acceptable to challenging recipients (long-waiters or highly sensitised).[24] In addition, several groups are exploring the use of normothermic machine perfusion to evaluate and optimise kidneys pre-implantation.[25] Kidneys with sub-optimal perfusion have been successfully evaluated and transplanted after a period of machine perfusion.[17, 26] Our data may help identify kidneys that could benefit from such 'rescue therapy'. This would particularly be valuable for grade 2-4 kidneys, where there is doubt regarding their viability.

The inconsistency in grading between retrieval and implanting teams is a concern, given the potential for inappropriate discard at the time of offering. For kidneys classified as having sub-optimal perfusion (grade 2-4) at retrieval, the majority were assigned a better grade by the implanting team. There are number of plausible explanations for this, including better exposure and flushing at implanting centre, discrepancies in the level of surgical experience and perhaps a natural bias of the implanting surgeon to document a better grade. Hosgood et al. and Mittal et al. observed similar variations in judgement when poorly perfused discarded kidneys were re-evaluated by experienced kidney transplant surgeons.[16, 17] This highlights the importance of re-assessment at the implanting centre, before the final decision is made to discard an organ, and the need for further standardisation and training on macroscopic assessment.

The main strength of this study is the large, consecutive sample size, resulting in sufficient statistical power to detect clinically meaningful effect sizes, and to allow for analysis of infrequently occurring outcomes, such as PNF. The cohort also included organs from both marginal and non-marginal donors, which should further improve generalizability relative to previous studies, which have tended to focus on hard-to-place kidneys with poor perfusion only.

There are a number of limitations to this study. Firstly, this grading scale is not validated, but instead represents real-world data and application of one aspect of donor kidney assessment in a national deceased-donor programme. A further limitation was the lack of a second assessment of perfusion for kidneys that were discarded. In some cases, these kidneys may have been discarded due to sub-optimal perfusion. Although this represents only 8.2% of all the kidneys analysed, it may have biased results based on recipient outcomes. Other more subtle retrieval related factors, such as inappropriate placement of the aortic cannula, degree of arterial atherosclerosis and time from in-situ perfusion to removal of kidney are not available for analysis, but may have influenced outcomes in some cases. In addition, changes to the retrieval service and allocation system over time (era effect) may have influenced outcomes. Finally, this data is not necessarily generalisable to other transplant programs, which may have different allocation policies, longer average cold ischaemia times, higher discard rates and differing retrieval practices. [27]

To conclude, our study has identified macroscopic assessment of the QOP as an important predictor of organ utilisation and graft outcomes, based on an existing grading system. Where there are concerns about perfusion at retrieval, we suggest that the organ is sent to a kidney unit with a view to further evaluation and/or optimisation. Urgent refinement, standardisation and validation of macroscopic scoring systems using a common language is required to prevent inappropriate discards.

# References


1. Stewart DE, Garcia VC, Rosendale JD, Klassen DK, Carrico BJ. Diagnosing the decades-long rise in the deceased donor kidney discard rate in the United States. Transplantation. 2017;101(3):575-87.
2. Singh SK, Kim SJ. Epidemiology of Kidney Discard from Expanded Criteria Donors Undergoing Donation after Circulatory Death. Clin J Am Soc Nephrol. 2016;11(2):317-23.
3. Mohan S, Chiles MC, Patzer RE, Pastan SO, Husain SA, Carpenter DJ, et al. Factors leading to the discard of deceased donor kidneys in the United States. Kidney Int. 2018;94(1):187-98.
4. Husain SA, Chiles MC, Lee S, Pastan SO, Patzer RE, Tanriover B, et al. Characteristics and Performance of Unilateral Kidney Transplants from Deceased Donors. Clin J Am Soc Nephrol. 2018;13(1):118-27.
5. Dare AJ, Pettigrew GJ, Saeb-Parsy K. Preoperative assessment of the deceased-donor kidney: from macroscopic appearance to molecular biomarkers. Transplantation. 2014;97(8):797-807.
6. Miret Alomar E, Trilla Herrera E, Lorente Garcia D, Regis Placido L, Lopez Del Campo R, Cuadras Sole M, et al. Systematic review of kidney transplantation functional predictors. Actas Urol Esp. 2018;42(4):218-26.
7. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88(2):231-6.
8. Stallone G, Grandaliano G. To discard or not to discard: transplantation and the art of scoring. Clin Kidney J. 2019;12(4):564-8.
9. Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. Lancet (London, England). 2013;381(9868):727-34.
10. Narvaez JRF, Nie J, Noyes K, Leeman M, Kayler LK. Hard-to-place kidney offers: Donor- and system-level predictors of discard. Am J Transplant. 2018;18(11):2708-18.

11. Ausania F, White SA, Pocock P, Manas DM. Kidney damage during organ recovery in donation after circulatory death donors: data from UK National Transplant Database. Am J Transplant. 2012;12(4):932-6.

12. Wigmore SJ, Seeney FM, Pleass HC, Praseedom RK, Forsythe JL. Kidney damage during organ retrieval: data from UK National Transplant Database. Kidney Advisory Group. Lancet (London, England). 1999;354(9185):1143-6.

13. Foundation E. Eurotransplant Manual Chapter 9 - Donor. 2016:37.

14. Ayorinde JOO, Hamed M, Goh MA, Summers DM, Dare A, Chen Y, et al. Development of an objective, standardized tool for surgical assessment of deceased donor kidneys: The Cambridge Kidney Assessment Tool. Clin Transplant. 2020;34(2):e13782.

15. Callaghan CJ, Harper SJ, Saeb-Parsy K, Hudson A, Gibbs P, Watson CJ, et al. The discard of deceased donor kidneys in the UK. Clin Transplant. 2014;28(3):345-53.

16. Mittal S, Adamusiak A, Horsfield C, Loukopoulos I, Karydis N, Kessaris N, et al. A Re-evaluation of Discarded Deceased Donor Kidneys in the UK: Are Usable Organs Still Being Discarded? Transplantation. 2017;101(7):1698-703.

17. Hosgood SA, Barlow AD, Dormer J, Nicholson ML. The use of ex-vivo normothermic perfusion for the resuscitation and assessment of human kidneys discarded because of inadequate in situ perfusion. J Transl Med. 2015;13:329.

18. Watson CJ, Johnson RJ, Birch R, Collett D, Bradley JA. A simplified donor risk index for predicting outcome after deceased donor kidney transplantation. Transplantation. 2012;93(3):314-8.

19. Berardinelli L, Beretta C, Raiteri M, Carini M. Early and long-term results using older kidneys from cadaver or living donors. Clin Transpl. 2001:157-66.

20. Tierie EL, Roodnat JI, Dor F. Systematic Surgical Assessment of Deceased-Donor Kidneys as a Predictor of Short-Term Transplant Outcomes. European surgical research Europaische chirurgische Forschung Recherches chirurgicales europeennes. 2019;60(3-4):97-105.

21. Hamed MO, Chen Y, Pasea L, Watson CJ, Torpey N, Bradley JA, et al. Early graft loss after kidney transplantation: risk factors and consequences. Am J Transplant. 2015;15(6):1632-43.

22. Mannon RB. Delayed Graft Function: The AKI of Kidney Transplantation. Nephron. 2018;140(2):94-8.

23. Moers C, Smits JM, Maathuis MH, Treckmann J, van Gelder F, Napieralski BP, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med. 2009;360(1):7-19.

24. Manook M, Koeser L, Ahmed Z, Robb M, Johnson R, Shaw O, et al. Post-listing survival for highly sensitised patients on the UK kidney transplant waiting list: a matched cohort analysis. Lancet (London, England). 2017;389(10070):727-34.

25. Kaths JM, Paul A, Robinson LA, Selzner M. Ex vivo machine perfusion for renal graft preservation. Transplant Rev (Orlando). 2018;32(1):1-9.

26. Georgiades F, Hosgood SA, Butler AJ, Nicholson ML. Use of ex vivo normothermic machine perfusion after normothermic regional perfusion to salvage a poorly perfused DCD kidney. Am J Transplant. 2019.

27. Ibrahim M, Vece G, Mehew J, Johnson R, Forsythe J, Klassen D, et al. An international comparison of deceased donor kidney utilization: What can the United States and the United Kingdom learn from each other? Am J Transplant. 2020;20(5):1309-22.

# Tables

**Table 1 – Multivariable analysis of predictors of organ discard**

| | Odds Ratio (95% CI) | P-Value |
|---|---|---|
| Quality of perfusion (retrieval team) | | **<0.001** |
| Grade 1 | - | - |
| Grade 2 | 2.13 (1.65 - 2.75) | **<0.001** |
| Grade 3 | 7.67 (5.44 - 10.82) | **<0.001** |
| Grade 4 | 3.79 (2.69 - 5.34) | **<0.001** |
| Machine perfusion | | **0.044** |
| No | - | - |
| Hypothermic | 0.64 (0.45 - 0.91) | **0.012** |
| Normothermic | 0.92 (0.20 - 4.28) | 0.913 |
| Donor Age (Years) | | **<0.001** |
| <40 | - | - |
| 40-49 | 1.50 (0.77 - 2.94) | 0.236 |
| 50-59 | 1.88 (0.97 - 3.65) | 0.061 |
| 60+ | 5.88 (2.77 - 12.49) | **<0.001** |
| Donor body mass index ($kg/m^2$) | | 0.082 |
| <18.5 | 1.50 (0.84 - 2.66) | 0.171 |
| 18.5-24.9 | - | - |
| 25.0-29.9 | 1.25 (1.04 - 1.50) | 0.018 |
| 30.0+ | 1.15 (0.92 - 1.43) | 0.212 |
| Donor history of hypertension | 1.64 (1.33 - 2.03) | **<0.001** |
| Donor Hepatitis C Virus (Positive) | 34.90 (17.03 - 71.53) | **<0.001** |
| Donor Cytomegalovirus (Positive) | 1.19 (1.02 - 1.38) | **0.030** |
| Donor cause of death | | **0.015** |
| Intracranial haemorrhage | - | - |
| Hypoxic brain damage | 1.12 (0.92 - 1.37) | 0.254 |
| Trauma | 0.64 (0.44 - 0.94) | **0.022** |
| Other | 1.26 (0.97 - 1.63) | 0.089 |
| Donor type (DCD) | 1.24 (1.01 - 1.52) | **0.041** |
| Donor liver retrieved | 0.65 (0.54 - 0.78) | **<0.001** |
| Donor terminal creatinine (mmol/L) | | **<0.001** |
| <60 | - | - |
| 60-74 | 1.09 (0.87 - 1.37) | 0.466 |
| 75-99 | 1.29 (1.04 - 1.61) | **0.021** |
| 100+ | 2.70 (2.18 - 3.35) | **<0.001** |

| | | |
|---|---|---|
| Donor last temperature (°C) | | **<0.001** |
| <36.0 | - | - |
| 36.0-36.4 | 0.63 (0.50 - 0.80) | **<0.001** |
| 36.5-36.9 | 0.91 (0.71 - 1.17) | 0.477 |
| 37.0+ | 0.72 (0.59 - 0.88) | **0.002** |
| Donor last systolic blood pressure (mmHg) | | **0.024** |
| <110 | - | - |
| 110-119 | 1.12 (0.88 - 1.42) | 0.347 |
| 120-134 | 1.02 (0.81 - 1.28) | 0.870 |
| 135+ | 1.33 (1.07 - 1.65) | **0.010** |
| Donor risk index score | | **<0.001** |
| <0.95 | - | - |
| 0.95-1.04 | 1.47 (0.75 - 2.90) | 0.259 |
| 1.05-1.49 | 0.82 (0.39 - 1.70) | 0.592 |
| 1.50+ | 0.68 (0.29 - 1.59) | 0.380 |

Results are from a multivariable binary logistic regression, using a backwards stepwise approach to variable selection. Factors considered for inclusion in the model are detailed in Supplementary Table 1. The final model was based on N=10,285 organs (N=851 discarded) after excluding cases with missing data for any of the factors considered. An alternative model, using a replace-with-mean approach to maximise the included sample size, is reported in Supplementary Table 2. Bold P-values are significant at P<0.05.

**Table 2a – Associations between donor/recipient factors and QOP assigned by the implanting team**

| | Total N | QOP – Implanting Team Grade 1 | Grade 2 | Grade 3 | Grade 4 | *P-Value* |
|---|---|---|---|---|---|---|
| ***Donor Factors*** | | | | | | |
| Age (Years) | 23035 | 50 (38-59) | 53 (43-62) | 53 (42-62) | 54 (44-63) | **<0.001** |
| Sex (% Male) | 23030 | 10430 (52.6%) | 1244 (56.9%) | 273 (59.0%) | 322 (59.9%) | **<0.001** |
| Ethnicity | 23001 | | | | | 0.886* |
| White | | 19055 (96.2%) | 2091 (95.6%) | 443 (95.7%) | 521 (96.7%) | |
| Asian | | 351 (1.8%) | 45 (2.1%) | 9 (1.9%) | 8 (1.5%) | |
| Black | | 191 (1.0%) | 27 (1.2%) | 7 (1.5%) | 5 (0.9%) | |
| Mixed/Other | | 215 (1.1%) | 24 (1.1%) | 4 (0.9%) | 5 (0.9%) | |
| Body mass index (kg/m$^2$) | 22372 | 25.5 (22.9-28.7) | 26.3 (23.7-30.0) | 26.0 (23.6-29.4) | 26.7 (23.9-30.2) | **<0.001** |
| Diabetes | 22416 | 1018 (5.3%) | 140 (6.6%) | 30 (6.6%) | 33 (6.3%) | **0.006** |
| Hypertension | 22182 | 4551 (23.8%) | 628 (30.1%) | 132 (29.7%) | 177 (34.2%) | **<0.001** |
| Smoking history | 22364 | 9358 (48.5%) | 1015 (47.8%) | 212 (46.9%) | 243 (47.2%) | 0.309 |
| Hepatitis C virus (Positive) | 22956 | 23 (0.1%) | 0 (0.0%) | 4 (0.9%) | 0 (0.0%) | 0.783 |
| Cytomegalovirus (Positive) | 22760 | 9807 (50.0%) | 1072 (49.8%) | 229 (49.9%) | 268 (50.0%) | 0.855 |
| Cause of death | 23035 | | | | | **<0.001*** |
| Intracranial haemorrhage | | 12536 (63.2%) | 1406 (64.3%) | 332 (71.6%) | 351 (65.1%) | |
| Hypoxic brain damage | | 3356 (16.9%) | 367 (16.8%) | 58 (12.5%) | 99 (18.4%) | |
| Trauma | | 2203 (11.1%) | 206 (9.4%) | 41 (8.8%) | 40 (7.4%) | |
| Other | | 1750 (8.8%) | 208 (9.5%) | 33 (7.1%) | 49 (9.1%) | |
| Type | 23035 | | | | | **<0.001** |
| DBD | | 14442 (72.8%) | 1329 (60.8%) | 301 (64.9%) | 307 (57.0%) | |
| DCD | | 5403 (27.2%) | 858 (39.2%) | 163 (35.1%) | 232 (43.0%) | |
| Liver retrieved | 23033 | 15320 (77.2%) | 1528 (69.9%) | 342 (73.7%) | 359 (66.6%) | **<0.001** |
| Adrenaline | 23035 | 1995 (10.1%) | 207 (9.5%) | 39 (8.4%) | 51 (9.5%) | 0.176 |
| Terminal creatinine (mmol/L) | 21393 | 75 (59-96) | 78 (60-101) | 81 (61-103) | 77 (61-103) | **<0.001** |
| Last temperature (°C) | 14125 | 36.6 (36.0-37.1) | 36.7 (36.0-37.4) | 36.8 (36.0-37.1) | 36.8 (36.0-37.4) | **<0.001** |
| Last systolic blood pressure (mmHg) | 15292 | 120 (109-134) | 120 (110-137) | 124 (112-143) | 123 (110-143) | **<0.001** |
| Last diastolic blood pressure (mmHg) | 15247 | 69 (60-78) | 70 (60-78) | 70 (60-80) | 69 (60-80) | 0.153 |
| Hospital stay (Days) | 22668 | 3.2** | 3.7** | 3.4** | 3.6** | **<0.001** |
| Donor risk index | 21646 | 1.04 (0.96- | 1.10 (0.99-1.51) | 1.09 (0.99-1.51) | 1.30 (1.01-1.55) | **<0.001** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 1.44) | | | | |
| ***Recipient Factors*** | | | | | | |
| Age (Years) | 23035 | 50 (40-60) | 52 (41-61) | 52 (43-61) | 52 (42-62) | **<0.001** |
| Sex (% Male) | 23026 | 12339 (62.2%) | 1439 (65.9%) | 310 (67.0%) | 361 (67.0%) | **<0.001** |
| Body mass index (kg/m$^2$) | 13257 | 25.9 (22.9 – 29.4) | 26.5 (23.3 – 29.9) | 27.2 (24.0 – 30.6) | 26.2 (23.0 – 29.9) | **<0.001** |
| Ethnicity | 22848 | | | | | 0.120* |
| White | | 15546 (79.0%) | 1706 (78.4%) | 353 (76.2%) | 439 (81.8%) | |
| Asian | | 2636 (13.4%) | 281 (12.9%) | 65 (14.0%) | 52 (9.7%) | |
| Black | | 1241 (6.3%) | 155 (7.1%) | 35 (7.6%) | 37 (6.9%) | |
| Mixed/Other | | 250 (1.3%) | 33 (1.5%) | 10 (2.2%) | 9 (1.7%) | |
| Diabetes | 23035 | 1495 (7.5%) | 198 (9.1%) | 31 (6.7%) | 59 (10.9%) | **0.005** |
| Hepatitis C virus (Positive) | 17340 | 109 (0.7%) | 12 (0.7%) | 3 (0.8%) | 2 (0.5%) | 0.660 |
| Cytomegalovirus (Positive) | 20650 | 9309 (52.5%) | 1053 (52.8%) | 224 (52.8%) | 254 (51.4%) | 0.934 |
| Waiting time (Days) | 23016 | 779 (325-1383) | 793 (354-1368) | 839 (422-1425) | 711 (314-1330) | 0.342 |
| Dialysis status at transplant | 20813 | | | | | **0.028*** |
| Haemodialysis | | 12455 (69.5%) | 1410 (71.8%) | 313 (72.0%) | 350 (72.3%) | |
| Peritoneal dialysis | | 5441 (30.3%) | 551 (28.1%) | 120 (27.6%) | 131 (27.1%) | |
| Pre-emptive | | 35 (0.2%) | 2 (0.1%) | 2 (0.5%) | 3 (0.6%) | |
| Calculated reaction frequency at transplant | 23035 | | | | | 0.555 |
| 0% | | 13306 (67.0%) | 1456 (66.6%) | 304 (65.5%) | 361 (67.0%) | |
| 1-85% | | 4874 (24.6%) | 545 (24.9%) | 123 (26.5%) | 131 (24.3%) | |
| >85% | | 1665 (8.4%) | 186 (8.5%) | 37 (8.0%) | 47 (8.7%) | |

Data are reported as median (IQR), with p-values from Jonckheere-Terpstra tests, or as N (%), with p-values from Kendall's tau, unless stated otherwise.

Bold p-values are significant at p<0.05. *p-Value from Chi-square test. **Reported as means to highlight the differences between groups.

**Table 2b – Associations between transplantation/organ factors and QOP assigned by the implanting team**

| | Total N | QOP – Implanting Team | | | | *P-Value* |
|---|---|---|---|---|---|---|
| | | ***Grade 1*** | ***Grade 2*** | ***Grade 3*** | ***Grade 4*** | |
| Damage to organ | 22873 | 2283 (11.6%) | 423 (19.5%) | 96 (20.8%) | 95 (17.8%) | **<0.001** |
| Transplant year | 23035 | | | | | **<0.001** |
| 2000-2004 | | 5115 (25.8%) | 436 (19.9%) | 99 (21.3%) | 78 (14.5%) | |
| 2005-2009 | | 4876 (24.6%) | 601 (27.5%) | 134 (28.9%) | 164 (30.4%) | |
| 2010-2013 | | 5075 (25.6%) | 651 (29.8%) | 130 (28.0%) | 168 (31.2%) | |
| 2014-2016 | | 4779 (24.1%) | 499 (22.8%) | 101 (21.8%) | 129 (23.9%) | |
| Number of renal arteries | 22963 | | | | | 0.192 |
| 1 | | 15769 (79.7%) | 1715 (78.8%) | 364 (78.4%) | 422 (78.4%) | |
| 2 | | 3636 (18.4%) | 418 (19.2%) | 90 (19.4%) | 109 (20.3%) | |
| 3+ | | 379 (1.9%) | 44 (2.0%) | 10 (2.2%) | 7 (1.3%) | |
| Number of centres offered | 7129 | | | | | 0.422 |
| 1 | | 4689 (76.6%) | 552 (79.5%) | 97 (68.3%) | 134 (78.8%) | |
| 2 | | 924 (15.1%) | 93 (13.4%) | 30 (21.1%) | 23 (13.5%) | |
| 3+ | | 510 (8.3%) | 49 (7.1%) | 15 (10.6%) | 13 (7.6%) | |
| Perfusate used | 22160 | | | | | **<0.001*** |
| Wisconsin | | 9929 (52.0%) | 1205 (57.3%) | 255 (57.2%) | 319 (61.0%) | |
| Marshalls | | 8949 (46.9%) | 878 (41.8%) | 190 (42.6%) | 200 (38.2%) | |
| Other | | 211 (1.1%) | 19 (0.9%) | 1 (0.2%) | 4 (0.8%) | |
| Machine perfusion | 21373 | | | | | 0.181* |
| No | | 17351 (94.2%) | 1906 (94.3%) | 407 (94.2%) | 470 (93.6%) | |
| Hypothermic | | 1025 (5.6%) | 113 (5.6%) | 25 (5.8%) | 28 (5.6%) | |
| Normothermic | | 41 (0.2%) | 3 (0.1%) | 0 (0.0%) | 4 (0.8%) | |
| Fast track | 23035 | 711 (3.6%) | 89 (4.1%) | 19 (4.1%) | 30 (5.6%) | **0.045** |
| Cold ischaemia time (hrs) | 22840 | 16.0 (12.8-19.6) | 15.8 (12.4-19.2) | 16.0 (13.0-19.9) | 15.6 (12.8-19.1) | **0.012** |
| Mismatch Level | 23034 | | | | | **<0.001** |
| 1 | | 2898 (14.6%) | 283 (12.9%) | 63 (13.6%) | 66 (12.2%) | |
| 2 | | 7495 (37.8%) | 715 (32.7%) | 130 (28.0%) | 198 (36.7%) | |
| 3 | | 8148 (41.1%) | 999 (45.7%) | 229 (49.4%) | 233 (43.2%) | |
| 4 | | 1303 (6.6%) | 190 (8.7%) | 42 (9.1%) | 42 (7.8%) | |

Data are reported as median (IQR), with p-values from Jonckheere-Terpstra tests, or as N (%), with p-values from Kendall's tau, unless stated otherwise.

Bold p-values are significant at p<0.05. *p-Value from Chi-square test.

**Table 3 – Associations between graft outcomes and quality of perfusion**

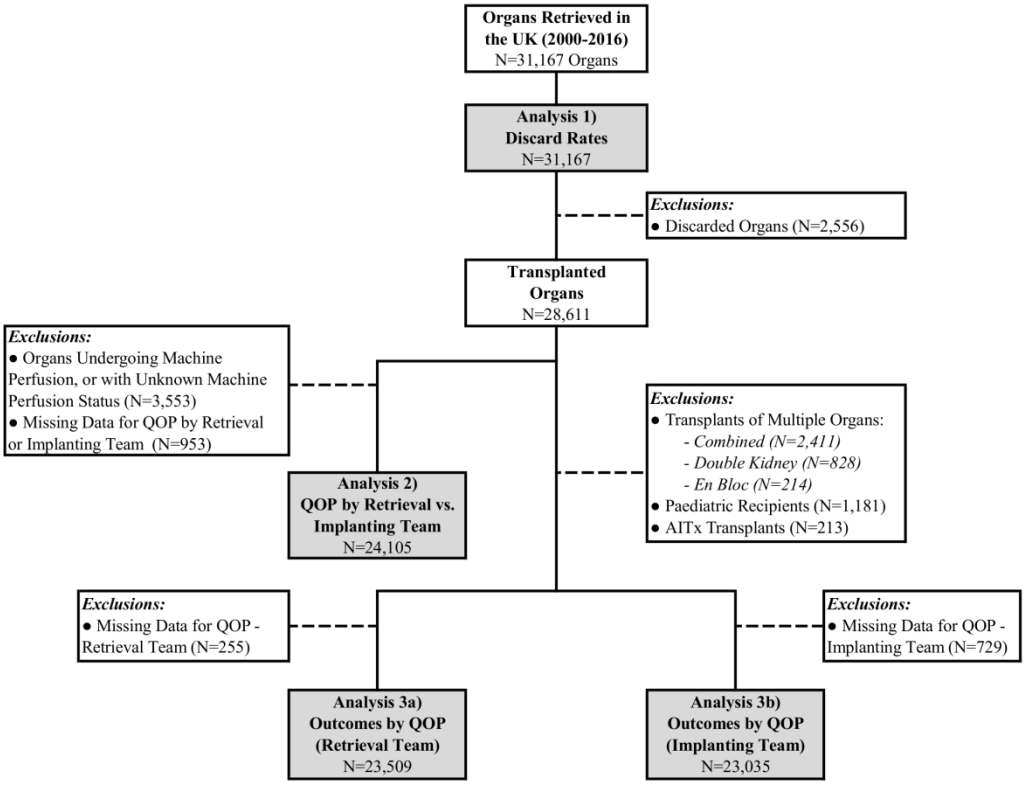
| | Total N | Quality of perfusion | | | | P-Value |
|---|---|---|---|---|---|---|
| | | Grade 1 | Grade 2 | Grade 3 | Grade 4 | |
| ***Quality of perfusion Assigned by Retrieval Team*** | | | | | | |
| Graft Function | 19489 | | | | | **<0.001** |
| Primary Function | | 12583(70.7%) | 644 (57.5%) | 110 (51.6%) | 199 (54.4%) | |
| Delayed graft function | | 4714 (26.5%) | 426 (38.0%) | 89 (41.8%) | 153 (41.8%) | |
| Primary non-function | | 493 (2.8%) | 50 (4.5%) | 14 (6.6%) | 14 (3.8%) | |
| Graft Survival | 23475 | | | | | **0.026** |
| Rate at five years | | 85.0% | 83.0% | 78.0% | 84.0% | |
| Long-Term Graft Survival* | 22383 | | | | | 0.454 |
| Rate at five years | | 88.6% | 87.9% | 83.6% | 88.9% | |
| Hazard ratio (95% CI) | | - | 1.04 (0.88-1.22) | 1.33 (0.93-1.90) | 1.05 (0.78-1.40) | |
| P-Value (vs. Grade 1) | | - | *0.655* | *0.123* | *0.752* | |
| ***Quality of perfusion Assigned by Implanting Team*** | | | | | | |
| Graft Function | 19158 | | | | | **<0.001** |
| Primary function | | 11801(71.9%) | 1069 (57.2%) | 206 (53.4%) | 239 (49.3%) | |
| Delayed graft function | | 4224 (25.7%) | 702 (37.5%) | 142 (36.8%) | 216 (44.5%) | |
| Primary non-function | | 392 (2.4%) | 99 (5.3%) | 38 (9.8%) | 30 (6.2%) | |
| Graft Survival | 23001 | | | | | **<0.001** |
| Rate at five Years | | 85.8% | 79.8% | 71.0% | 78.5% | |
| Long-Term Graft Survival* | 21948 | | | | | **<0.001** |
| Rate at five Years | | 88.9% | 85.4% | 82.4% | 86.6% | |
| Hazard ratio (95% CI) | | - | 1.28 (1.15-1.42) | 1.43 (1.15-1.79) | 1.12 (0.90-1.39) | |
| P-Value (vs. Grade 1) | | - | ***<0.001*** | ***0.001*** | *0.326* | |

Categorical outcomes are reported as N (%), with p-values from Chi-square tests. Survival outcomes are reported as Kaplan-Meier estimated rates at five years, as well as hazard ratios with 95% confidence intervals from univariable Cox regression models, relative to QOP grade 1. *Long-term graft survival excluded patients with graft failure or loss of follow up within 30 days, to negate the difference in PNF between the groups. Bold p-values are significant at p<0.05.

**Table 4 – Summary of multivariable analyses by quality of perfusion**

| Outcome | Type of Model | Included N | | Overall P-Value | Quality of perfusion | | | |
|---|---|---|---|---|---|---|---|---|
| | | Total | Outcomes | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| **Quality of perfusion assigned by retrieval team** | | | | | | | | |
| Delayed graft function* | BLR | 10,160 | 2,841 | **0.019** | - | **1.28 (1.06 - 1.54) (P=0.009)** | 1.24 (0.83 - 1.84) (P=0.292) | 1.31 (0.96 - 1.78) (P=0.090) |
| Primary non-function | BLR | 7,794 | 465 | **0.001** | - | **1.66 (1.19 - 2.32) (P=0.003)** | **2.54 (1.32 - 4.89) (P=0.005)** | 1.34 (0.71 - 2.55) (P=0.371) |
| Long-term graft survival** | CR | 12,342 | 2,028 | 0.111 | - | 0.97 (0.77 - 1.22) (P=0.811) | 1.79 (1.10 - 2.89) (P=0.018) | 1.14 (0.76 - 1.71) (P=0.529) |
| **Quality of perfusion assigned by implanting team** | | | | | | | | |
| Delayed graft Function* | BLR | 18,599 | 5,284 | **<0.001** | - | **1.50 (1.34 - 1.67) (P<0.001)** | **1.54 (1.22 - 1.94) (P<0.001)** | **2.08 (1.69 - 2.54) (P<0.001)** |
| Primary non-function | BLR | 19,158 | 559 | **<0.001** | **-** | **2.02 (1.60 - 2.54) (P<0.001)** | **3.65 (2.55 - 5.23) (P<0.001)** | **2.42 (1.64 - 3.57) (P<0.001)** |
| Long-term graft survival** | CR | 21,955 | 3,526 | **0.002** | - | **1.18 (1.06 - 1.31) (P=0.003)** | **1.36 (1.09 - 1.69) (P=0.007)** | 1.04 (0.83 - 1.29) (P=0.749) |

Results are from multivariable binary logistic regression (BLR), or Cox regression (CR) models, as applicable. A backwards stepwise approach was used for variable selection, and the full list of factors considered for inclusion are detailed in Table S1. The analyses reported for the QOP assigned by the retrieval team use a complete cases approach, whilst analysis of the QOP assigned by the implanting team use a replace-with-mean approach. The full models, and further details about the methodology are reported in Tables S3a-c and S4a-e. Data are reported as odds ratios (BLR) or hazard ratios (CR) with 95% CIs, and bold p-values are significant at p<0.05. *Analyses of DGF exclude patients with PNF. **For graft survival, patients with graft failure or loss of follow up within 30 days were excluded, to negate the difference in PNF between the groups. DGF/PNF – delayed graft function/primary non-function

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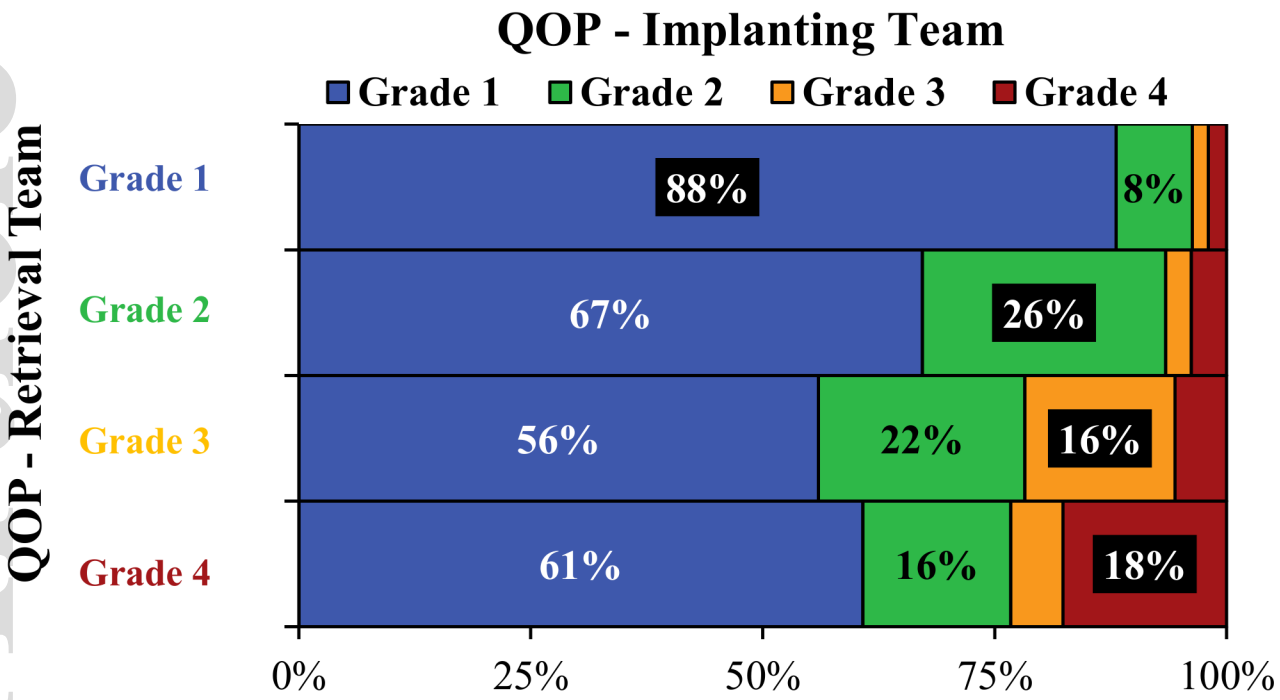


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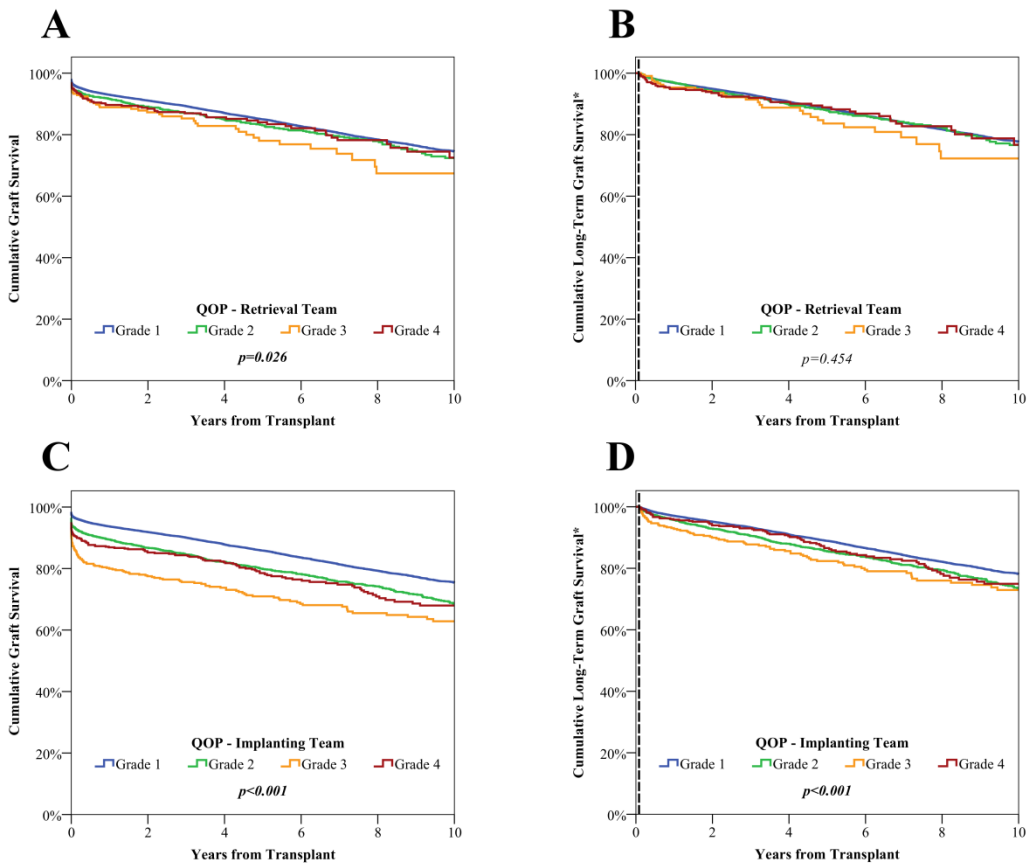


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